UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	5

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

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1- File Copy

PTO-90C (Rev. 2/95)

US GPO 2000 . 465-188/25266

Office Action Summary	Application No.	Applicant(s)	
	09/472,558	BAHRAMIAN ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *28-49, 51, and 53-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27, 50, and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 11-27, drawn to a method for muting a nucleic acid sequence, classified in classes 435 and 800, subclasses 455 and 21 respectively.

II. Claims 28-35, drawn to a method for identifying a muting nucleic acid sequence, classified in class 435, subclass 6.

III. Claims 36-41, drawn to a method of identifying a phenotype, classified in class 435, subclasses 455, 463.

IV. Claims 42-49, and 51, drawn to a method of screening, classified in class 435, subclass 455.

V. Claims 53-56, drawn to a kit for identifying a muting nucleic acid, classified in class 536, subclass 23.1.

Claims 1-10, 50, and 52 are generic to all the groups.

Inventions I-IV and V are related as process and apparatus for its practice. The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (MPEP § 806.05(e)). In this case the process as claimed can

be practiced by another materially different apparatus or by hand. The methods of groups I-IV can be used with different reagents. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and requirement for separate searchs, restriction for examination purposes as indicated is proper.

Although there are no provisions under the section for "Relationship of Inventions" in MPEP 806.05 for inventive groups that are directed to different methods, restriction is deemed to be proper between groups I, II, III, and IV because their methods appear to constitute patentably distinct inventions, each with a distinct purpose and further comprising distinct methodologies and using different products. Because these inventions are distinct for the reasons given above and a separate search is required for each of Groups I, II, III, and IV, restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

During a telephone conversation with Sonia Guterman on 7/5/00 a provisional election was made without traverse to prosecute the invention of group I, claims 11-27. Affirmation of this election must be made by applicant in replying to this Office action. Claims 28-49, 51, and 53-56 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-10, 50, and 52 are generic to each group and will be examined accordingly.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

Claim 17 is objected to because of the following informalities: it appears that the term "portion" should be plural. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-27 contain indefinite language. The term "muting" does not convey a clear meaning. It is not clear from the claims as they are written if the expression of the "muted" gene is completely abolished or only reduced.

Claims 12, 17-18, and 22-23 contain indefinite language. The term "substantially homologous" does not convey any clear meaning. It is not clear how homologous the muting transgene must be to the endogenous gene. Will a nucleic acid sequence with any amount homology to the endogenous sequence function as a muting transgene?

Claims 26-27 contain indefinite language. The term "substantially integrated" does not convey any clear meaning. It is not clear how a plasmid can be only partially integrated. A plasmid can either be integrated or not integraged.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-27, 50 and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a knockout mouse, comprising embryonic stem (ES) cells which have been genetically modified,such that expression of an endogenous gene has been reduced, using a muting transgene, does not reasonably provide enablement for a method of producing a knock-out animal of any and all species comprising ES cells which have been genetically modified by a muting transgene or a pharmaceutical composition comprising a nucleic acid composition. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 11 is directed to a method for muting expression of an endogenous gene in an animal cell, comprising delivering a muting nucleic acid to a cell. Claim 12 is directed to the same method wherein the muting nucleic acid is homologous to a sequence in the endogenous gene. Claim 13 is directed to the same method wherein the nucleic acid is DNA, RNA, or a nucleic acid analog. Claims 14-15 are directed to the same method wherein the nucleic acid is engineered into a vector, in particular a plasmid, phagemid, or a virus. Claim 16 is directed to the same method wherein the vector is a double-stranded DNA plasmid. Claim 17 is directed to the same method wherein the muting sequence of the transgene is homologous to 5' untranscribed region, the coding region, the 3' untranscribed region, the 3' untranslated, or a region which overlaps 2 adjacent ends of 2 portions of the endogenous gene. Claims 18-21 are directed to the same method wherein the muting nucleic acid sequence is homologous to a region of the 5' end of the endogenous gene, particularly to a region which is 200-400 bases, 400-600 bases, or 600-1000 bases in length. Claims 22-23 are directed to the same method wherein the muting nucleic acid is homologous to a region of the 3' end or to a region which overlaps the 3'coding region and an untranscribed region of the endogenous gene. Claim 24 is directed to the same method wherein the delivery of the muting acid is accomplished by transformation, transfection, electroporation, infection, or lipofection. Claim 25 is directed to delivery of the muting nucleic acid by infection. Claims 26-27 are

directed to the same method wherein the plasmid containing the muting nucleic acid is transiently maintained in the cell. Claims 50 and 52 are directed to nucleic acid compositions.

The specification teaches a method of muting expression of an endogenous gene, pro-a1(I) collagen, of a rat fibroblast cell line in vitro using a muting nucleic acid sequence, particularly a full length pro-a1(I) collagen gene which has been inserted into a plasmid. Claims 11-27 read on a method of creating a knockout mammal as interpreted in light of the teachings of the specifcation (see specification page 3 line 6, also page 4 lines 18-20). The art of creating knockout mice using ES cell technology is well known, such that a knockout or muting transgene could be made for any known gene of interest.

With regard to claim breadth, the standard under 112, first paragraph entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, in light of the specification, the claimed invention is properly interpreted with regard to a method of creating knock-out mammals. Such an interpretation is consistent with the specification despite that the claimed non-human mammals require only that they lack a functional endogenous gene which has been muted with a muting transgene. This is because, with regard to the enablement requirement, one of skill in the art must be provided with both how to make and use the claimed invention. As such, the enabled scope of the

claimed invention, in light of the teachings of the specification, is found to be the generation of transgenic knockout mice, comprising a muting transgene.

Furthermore, with regard to the claimed breadth directed to methods of producing any and all transgenic non-human mammals, it is well known in the knockout art that the production of knockout animals other than mice is undeveloped. This is because ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species. See Moreadith et al. (J. Mol. Med., 1997) at page 214, Summary. Seamark (Reproductive Fertility and Development, 1994) supports this observation by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Likewise, Mullins et al. (Journal of Clinical Investigation, 1996) state that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page S38, column 1, first paragraph). As the claims are directed to a transgenic non-human mammal lacking a functional calcineurin gene which must be generated by the introduction of a transgene into an ES cell, the state of the art supports that only mouse ES cells were available for use for production of transgenic mice.

If the intention is to read the claims on a method of producing transgenic animals then steps which are essential for the production of same animals are missing from the claims (this interpretation is based on the teachings of the

specification page 3, paragraph bridging to page 4). The claims should be amended to include all necessary steps for producing transgenic animals.

Claims 26-27 read on the same method, wherein the transgene is not fully integrated in the host chromosome and is only transiently expressed. In light of the interpretation of claims as discussed above, it would **not be possible** to create a knockout mouse which did not comprise an integrated transgene. The state of the art suggests that it would be unpredictable to expect to mute expression of any endogenous gene in a mouse without integration or stable expression of a muting transgene and the specification lacks guidance for muting nucleic acid sequences by somatic gene transfer as it lacks any relevant teachings regarding routes of administration and cell targeting critical to achieving muting of any particular nucleic acid sequence of interest. In view of the quantity of experimenation necessary, it would be unpredictable for one of skill in the art to make and use a knockout mouse which did **not** comprise an integrated transgene (muting, knockout, or targeting).

Claims 11-27, 50 and 52 read on gene therapy of any and all diseases using the using a pharmacuetical composition comprising a muting nucleic acid composition or a nucleic acid composition capable of alleviating a muted gene. Although the claimed methods are not limited to any particular application requiring any particular therapeutic effect, with regard to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are

to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest reasonable interpretation of the claimed invention encompasses a method for expressing a therapeutic gene in a cell of a host to achieve expression of the gene at a level resulting in a therapeutic effect and a composition which provides therapy (see specification, page12, whole page). However, the specification fails to enable methods using any disclosed pharmaceutical composition for gene therapy.

The only working example provided by the specification, a method of muting expression of an endogenous gene, pro-a1(I) collagen, of a rat fibroblast cell line in vitro using a muting nucleic acid sequence, particularly a full length pro-a1(I) collagen gene which has been inserted into a plasmid. As such the working example fails to demonstrate a viable correlation to gene therapy due to a lack of an in vivo working model which can show a therapeutic effect in response to administration of the same pharmaceutical composition.

The state of the art of gene therapy is unpredictable with respect to treatment of any and all diseases. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by two subsequently published reviews. Verma *et al.* teach that as of 1997, "there is still no single outcome that we can point to as a success story" (page 239, col. 1). The authors go on to state, "Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (page 239, col. 3). Anderson (1998) states that

"there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (page 25, col 1) and concludes, "Several major deficiencies still exist including poor delivery system, both viral and no-viral, and poor gene expression after genes are delivered" (page 30). Besides the general expectation that it will require years of further research to develop effective gene therapy (Anderson, page 30), it would require extensive research to understand the fundamental biology of the system. Thus in view of the lack of guidance and direction provided by the specification for gene therapy of any and all diseases, it would have required one of skill in the art undue experimentation to make and use the invention as claimed.

Accordingly, in view of the quantity of experimentation necessary for the production and use of any and all non-human mammals lacking any and all functional endogenous genes, the lack of direction or guidance, as well as the absence of working examples, provided by the specification for the production and use of any and all non-human knockout mammals other than transgenic knockout mice, the lack of guidance or direction, as well as the absence of working examples provided by the specification for gene therapy of any and all diseases, the unpredictable and undeveloped state of the art for the production of transgenic non-human knockout mammals, particularly with respect to the unpredictable nature of the phenotypic effect, the unpredictable and undeveloped state of the art of gene therapy, the breadth of the claims encompassing any and all non-human mammals lacking any and all functional endogenous genes, and the breadth of the claims with regard to gene therapy of any and all diseases, it

would have required undue experimentation for one skilled in the art to make and/or use the claimed non-human mammals and pharmaceutical compositions.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-17 and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Capecchi et al (March 1994, Scientific American, 52-59).

. Claim 1 is directed to a nucleic acid composition for muting expression of a gene in an animal cell wherein muting nucleic acid includes a sequence homologous an endogenous sequence in the gene. Claims 2-3 are directed to the same nucleic acid composition wherein gene is located on a chromosome of the cell, in particular when the cells contain a gene of a pathogen or are cancer or autoimmune cells. Claim 4 is directed to the same composition wherein the pathogen is a virus. Claim 5 is directed to the same composition wherein the nucleic acid is DNA, RNA, or a nucleic acid analog. Claim 6 is directed to the same composition wherein the nucleic acid analog is phosphorothioate, 2'-o-methyl RNA or a peptide nucleic acid. Claim 7 is directed to the same composition wherein the nucleic acid is double-stranded DNA. Claims 8-10 are directed to the same nucleic acid composition wherein the animal is a vertebrate,

particularly warm-blooded and a mammal. Claim 11 is directed to a method for muting expression of an endogenous gene in an animal cell, comprising delivering a muting nucleic acid to a cell. Claim 12 is directed to the same method wherein the muting nucleic acid is homologous to a sequence in the endogenous gene. Claim 13 is directed to the same method wherein the nucleic acid is DNA, RNA, or a nucleic acid analog. Claims 14-15 are directed to the same method wherein the nucleic acid is engineered into a vector, in particular a plasmid, phagemid, or a virus. Claim 16 is directed to the same method wherein the vector is a double-stranded DNA plasmid. Claim 17 is directed to the same method wherein the muting sequence of the transgene is homologous to 5' untranscribed region, the coding region, the 3' untranscribed region, the 3' untranslated, or a region which overlaps 2 adjacent ends of 2 portions of the endogenous gene. Claims 22-23 are directed to the same method wherein the muting nucleic acid is homologous to a region of the 3' end or to a region which overlaps the 3'coding region and an untranscribed region of the endogenous gene. Claim 24 is directed to the same method wherein the delivery of the muting acid is accomplished by transformation, transfection, electroporation, infection, or lipofection.

Capecchi et al teach a knockout construct for the murine *Hox*A-3 gene and a method of inserting the knockout construct into embryonic stem cells to knockout the endogenous Hox A-3 gene (and suggest that this technology can be directed to any known gene of interest in the mouse). Capecchi teach the essential components of the knockout construct (which is a double-stranded DNA

plasmid comprising homologous regions of the known gene sequence that flank a neomycin resistance gene), discussing that different regions of the known gene can be incorporated into the knockout construct. See page 54, column 3; and page 55, columns 1 & 2. The knockout construct can be delivered into the embryonic stem cells by electroporation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 8-10, 12, 17-21, and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (March 1994, Scientific American, 52-59).

Claim 1 is directed to a nucleic acid composition for muting expression of a gene in an animal cell wherein muting nucleic acid includes a sequence homologous an endogenous sequence in the gene. Claims 8-10 are directed to the same nucleic acid composition wherein the animal is a vertebrate, particularly warm-blooded and a mammal. Claim 12 is directed to the same method wherein the muting nucleic acid is homologous to a sequence in the endogenous gene. Claim 17 is directed to the same method wherein the muting sequence of the

transgene is homologous to 5' untranscribed region, the coding region, the 3' untranscribed region, the 3' untranslated, or a region which overlaps 2 adjacent ends of 2 portions of the endogenous gene. Claims 18-21 are directed to the same method wherein the muting nucleic acid sequence is homologous to a region of the 5' end of the endogenous gene, particularly to a region which is 200-400 bases, 400-600 bases, or 600-1000 bases in length. Claim 25 is directed to delivery of the muting nucleic acid by infection. Claims 26-27 are directed to the same method wherein the plasmid containing the muting nucleic acid is transiently maintained in the cell.

Capecchi teaches knockout technology applied to mice specifically with respect to the disruption of the *Hox*A-3 gene and as the method of producing the same applies to determining the *in vivo* biological function of **any** known gene of interest. For example, Capecchi discloses the applicability of gene targeting to many other genes so that a correlation can be drawn between the malfunctioning of the gene to the manifestation of disease. Capecchi further discloses the **essential** components of a targeting vector (page 54, column 3; and page 55, columns 1 & 2), and the steps involved for targeted gene replacement in ES cells as well as in mice (pages 55-56 and diagrams).

Capecchi differs from the claimed invention in that lengths of the homologous regions of the endogenous gene to be used in the targeting construct as well as somatic gene targeting in mice are not specifically discussed.

Accordingly, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the knockout technology of Capecchi by use of a targeting vector (which could include 5' end of the endogenous gene 600-1000 bases in length) for disruption of known endogenous genes in a mouse (in both somatic and embryonic stem cells) with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at 703-308-2035. The FAX phone number for art unit 1632 is 703-308-0294.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Peter Paras, Jr.

Art Unit 1632